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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,297	08/24/2005	Joseph Alexander Lasky	ON/4-32744A	1063

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
05/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/532,297	LASKY, JOSEPH ALEXANDER	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 May 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *12 May 2009*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: *10*.
   Claim(s) rejected: *2,5,7 and 10*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614

/Timothy P Thomas/
Examiner, Art Unit 1614

Continuation of 3. NOTE: Claim 10 has been amended to remove a claim limitation of a time period exceeding three months, a time period that has been introduced into new claim 11, without cancelation of any other finally rejected claim; additionally the removal of the claim limitation requires additional consideration as to whether a rejection under 35 USC 102 may be applicable; such a rejection is of record, but was not maintained in the final Office Action, based on the addition of the same specific limitation to claim 10.

Continuation of 11. does NOT place the application in condition for allowance because: The rejections of record are maintained for the reasons of record.

Applicant argues that the present final rejection is premature, and requrest withdrawl of the finality of the rejection; that claim 4 was present in the application at the time that the prior art rejection was made and there was no indication that Applicant intended to abandon the subject matter; that every claim from which claim 4 could have properly depended related to and required the administration of imatinib to a patient for the treatment of pulmonary hypertension; that applicant understood not including claim 4 in the art rejection to mean that claim 4 was patentable over the prior art and that the art rejection could be overcome by limiting the main claim to the scope set forth in claim 4. This argument is not persuasive. Claim 4 of the 9/27/2007 claim amendment depended on a canceled claim (claim 3). As such claim 4 did not even recite any compound or disease. In such a case, the proper rejection is that the subject matter of the claim was unclear; accordingly the claim was rejected under 35 USC 112, 2nd paragraph as indefinite. Inclusion of claim 4 in any prior art rejection would have been improper, since there was no step recited involving any compound or disease or patient population limitations. The fact that the claim was not included in the prior art rejection was not related to the patentablity of the claim over the prior art; but that the subject matter was unclear. Applicant was clearly informed that the claim subject matter was indefinite (see p. 2, Item 4 of the 4/1/2008 Office Action).

Applicant argues some points about what would have occurred "if" the claim had been corrected, and that such a rejection would have been a new rejection basis, that should not have been made final. It is unclear what the point of this argument is. Such a scenario is not the case. Therefore the finality of the 1/12/2009 Office Action is not withdrawn.

With respect to the enablement rejection, applicant argues that the examiner states the specification is enabling for curative treatment, but not for prophylactic treatment; but the examiner has provided no scientific rationale to explain why a compound which has efficacty for treating ongoing episodes of the condition would not also prevent the onset or recurrence of the condition. To clarify the record, curative treatment with the traditional meaning of completely getting rid of the ailment is not considered enabled. Only when the term "curative" is taken with the meaning of "having efficacy with respect to episodes of pulmonary hypertension"; i.e., a reduction in hypertention levels, falling within the scope of claim 10, is such an embodiment of treatment considered enabled. Reducing levels of pulmonary hypertension is not identical to the complete removal of pulmonary hypertension (which would be required by the usual definition of "cure").

In contrast, the broadest reasonable definition of prevention implies that the condition will not occur upon the administration of the elected compound, irrespective of the cause of the pulmonary hypertension processes. The argument that no scientific rationale has been provided is not persuasive; such rationale was laid out in the Office Action of 4/1/2008; which clearly discussed that the state of the art indicates that PAH is a disease with poor prognosis, with a precise mechanism that still remains to be elucidated. While some drugs are currently used in treatment, more effective treatment still needs to be developed; unknown triggers contribute to the development of pulmonary hypertention. Taken with the data of the specification, where 80% reduction in levels of pulmonary hypertension in rats has been disclosed, this provides evidence in support of reducing the pulmonary blood pressure levels, but not the complete removal of the disease nor prevention of the disease. Prevention requires more than reduction in pulmonary arterial blood pressure levels; it requires that the condition will not occur as a result of the administration of the claimed drug, even in the presence of known or unknonw disease triggers that normally lead to the development of the disease. The embodiment within the claims of prevention is still considered to require undue experimentation to practice the invention.

With respect to the rejection under 35 USC 103, applicant argues that: 1) the references do not implicate PDGRF in pulmonary hypertension, but merely report on pathways involving PDGFR activity may be related to pulmonary hypertention or that PDGFR is overexpressed in PH, but neither suggests PDGFR inhibition as a therapy to control PH. This is not persuasive; as present on the record, Goncharova indicates that targeting PI3K-dependent human PVSM cell motility and proliferation may offer a potential target in blocking development of hypertension (p. L362, last paragraph); the references imply the relationship that exists between PDGFR activity and pulmonary hypertension, would lead to the expectation that reduction of such activity (i.e., by inhibition of PDGFR) would reduce the contribution of this pathway to pulmonary hypertension

2) Goncharova does not teach that imatinib inhibits cell proliferation and motility, but rapamycin has these properties; that Goncharova teaches S6K1 plays a potentially important role in PSVM cell mitogenesis and that PVSM cell proliferation demonstrates high sensitivity to rapamycin, a specific inhibitor of S6K1; i.e., Goncharova leads the skilled artisan to take a different approach. The fact that, for example, Goncharova teaches cell proliferation and motility is a critical step in vascular remodeling (important in diseases including pulmonary hypertension), coupled with Zimmerman, which teaches diseases with vascular smooth-muscle cell migration and proliferation where PDGR and PDGF-R often play a role, such as restenosis and artherosclerosis (Zimmerman, p. 17, 1st paragraph), is an indication that both rapamycin and imatinib have the same art recognized properties of inhibition of cell migration and proliferation, which play important roles in progression of pulmonary hypertension. Therefore it would have been obvious to utilize imatinib in treating pulmonary hypertension. Applicant is referred to MPEP 2144.06 (II), that indicates it would be obvious to substitute equivalents known for the same purpose (imatinib for rapamycin, both with cell migration and proliferation inhibiting activity, in this case).

3) Tanabe describes experiments which suggest that PDGFR may play a role in vasulature hypertensive diseases, but does not reach the conclusion that inhibiting PDGFR may provide a therapeutic benefit for such diseases; that Tanabe describes experiments that lead to the conclusion that stretch triggers the overexpression of PDGFRbeta in vasculature hypertensive diseases; thus PDGFR system may play a significant role in the development of several hypertensive diseases; this report is only a report of experiments that suggest a correlation between PDGF-Rbeta and vasculature hypertensive diseases, such as pulmonary hypertension, but does not suggest that the inhibition of PDGFR as an appropriate treatment for the condition. One of ordinary skill in the art would have had the expectation that inhibiting

PDGFR would lead to the reduction of the extent of pulmonary hypertension disease process based on the correlations of Tanabe, in part, and for the reasons of record: 1) both Goncharova and Tanabe implicate the role of PDGF-R in pulmonary hypertension and Zimmerman teaches imatinib is useful in diseases where PDGF-R plays a role; 2) Gocharova teaches cell proliferation and motility is a critical step in vascular remodeling, imatinib inhibits such processes; and 3) Tanabe teaches phosphorylation of PDGF receptor β by stretch in endothelial cells is a component of pulmonary hypertension, such phorsphorylation is inhibited by imatinib. These points taken together, lead to a reasonable expectation of success in reducing the progress of the disease, i.e., in treating pulmonary hypertension by administration of imatinib.

Applicant further argues that the references do no more than suggest a connection between PDGFR and pulmonary hypertension; which is merely an invitation to experiment which provides no basis to have a reasonable expection that PDGFR inhibition would be useful for the treatment of pulmonary hypertension; that the combined disclosure would not lead to the present inbention, but to experiment with S6K1 inhibitors like rapamycin, not PDGFR inhibitors. The connection between PDGFR and pulmonary hypertension that has been established would lead to a reasonable expectation of reducing the effect of high levels of PDGFR activity, a condition that is associated with pulmonary hypertension, and the detrimental effects of, for example vascular remodeling, and the stretch induced phosphorylation processes. Both of these lead to the expectation of a benefit in treatment of pulmonary hypertension disease progression. With respect to rapamycin, this argument has been addressed above.